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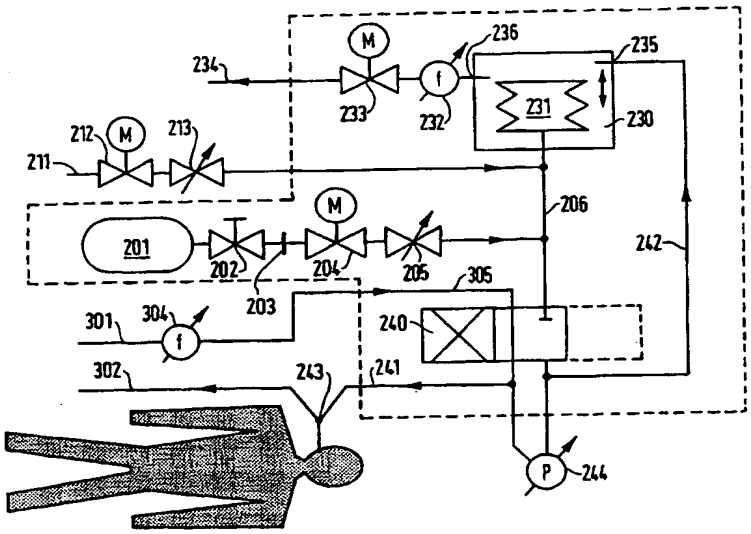

(57) Abstract

The invention provides an apparatus for fluid administration comprising: a variable volume fluid reservoir and a fluid conduit leading therefrom to a fluid outlet, a first fluid inlet and a second fluid inlet; a first detector arranged to detect fluid flow between said conduit and said reservoir; a first valve arranged to permit or prevent fluid flow from said first inlet through said conduit into said reservoir; a second valve which in a first setting permits fluid flow from said second inlet through said conduit to said outlet and prevents fluid flow from said reservoir through said conduit to said outlet and in a second setting permits fluid flow from said reservoir through said conduit to said outlet and prevents fluid flow from said second inlet through said conduit to said outlet; a second detector arranged to detect fluid flow into said conduit from said second inlet; and an activator arranged to control the operation of said first and second valves.

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APPARATUS FOR FLUID ADMINISTRATION

This invention relates to a device (hereinafter an "applicator") suitable for the delivery of a fluid bolus, e.g. a bolus of a liquid or gas, optionally containing an entrained discontinuous phase, for example solid particles, liquid droplets, vesicles (e.g. micelles, liposomes, microbubbles, microballoons, etc) and the like. In particular, the applicator is suitable for the delivery of a gas bolus into the respiratory system of a human or an air-breathing animal (e.g. mammal, reptile or bird). More especially the applicator is suitable for the delivery of a bolus of a hyperpolarized gas.

In magnetic resonance imaging (MRI), an image of the subject under study is generated using the nuclear magnetic resonance signal from non zero nuclear spin nuclei within the subject. In conventional MRI, the nuclei (the "imaging nuclei") responsible for the signal are protons, generally water protons. The strength of the MR signal is proportional to the population difference (the polarization) between the different nuclear spin states of the imaging nuclei and this in turn is governed by a Boltzmann distribution and is dependent on the magnetic field and temperature. The equilibrium polarization P_o for an I=½ imaging nucleus is given by the equation

$$P = \left| \frac{N\alpha - N\beta}{N\alpha + N\beta} \right| = \frac{1 - \exp(-\gamma\hbar B_o / kT)}{1 + \exp(-\gamma\hbar B_o / kT)} = \tanh(-\gamma\hbar B_o / kT)$$

which approximates to

$$P_o \simeq \frac{\mu B_o}{kT}$$

where $N\alpha$ is the population for nuclei in one spin state α (e.g. +½);

N_β is the population for nuclei in the other spin state β (e.g. -½);

γ is the magnetogyric ratio for the nucleus;

$\hbar$ is Planck's constant divided by 2π;

k is Boltzmann's constant;

B_o is the magnetic field (or magnetic flux density);

T is temperature in Kelvin; and

μ is the magnetic core dipole moment.

Recently, it has been found to be possible to increase MR signal strength by polarizing (hyperpolarizing) the imaging nuclei to a polarization value higher than the equilibrium value for the field strength and operating temperature of the MR imaging apparatus.

One way to achieve hyperpolarization is optical pumping of ^{3}He (see for example Schearer et al. Phys. Rev. Letters 10: 108-110 (1963), and Eckert et al. Nucl. Instr. and Methods A320: 53-65 (1992)). ^{3}He has a nuclear spin I of ½ and this can be used as the imaging nuclei in MRI (see for example US-A-5642625, US-A-5612103, US-A-5545396, WO95/27438, WO97/37239, Song et al. J. Mag. Res. A 115: 127-130 (1995) and Middleton et al. Mag. Res. Med. 33: 271-275 (1995)).

In general in ^{3}He MRI, a bolus of hyperpolarized ^{3}He is delivered into the respiratory tract of the subject, e.g. into the trachea, lungs, and alveolar space, and an MR signal from the ^{3}He is used to generate an image of the lungs. Since the natural occurrance of ^{3}He elsewhere in the body is negligible, there is negligible signal from regions in the body other than the respiratory tract.

Helium atoms have different properties to the oxygen and nitrogen molecules that make up the majority of the air that the subject normally breathes, e.g. in terms of ability to diffuse, and if the ^{3}He bolus is not

to distribute in the respiratory tract significantly differently from air, it is desirable to ensure that it makes up only a relatively small proportion of the total breath intake.

Moreover, if the ^{3}He bolus can be delivered at different stages of the breath intake, it is possible to generate MR images which emphasise different parts of the respiratory tract, e.g. alveolar space or trachea.

Furthermore, it is convenient to manufacture and supply the hyperpolarised gas in quantities significantly greater than the quantity required for generation of a single image and thus it is desirable to be able to make gas boli of reproducible size using a source of hyperpolarised gas containing a much larger amount of the gas. High levels of reproducibility, both in terms of bolus size and placement, are desirable for systematic clinical studies and protocols.

Thus there is a need for a device that can deliver a bolus of hyperpolarized ^{3}He of a desired volume into a subject's breath intake at a desired point in breath intake.

Viewed from one aspect the invention provides an apparatus for fluid administration comprising:

a variable volume fluid reservoir and a fluid conduit leading therefrom to a fluid outlet, a first fluid inlet and a second fluid inlet; a first detector arranged to detect fluid flow between said conduit and said reservoir; a first valve arranged to permit or prevent fluid flow from said first inlet through said conduit into said reservoir; a second valve which in a first setting permits fluid flow from said second inlet through said conduit to said outlet and prevents fluid flow from said reservoir through said conduit to said outlet and in a second setting permits fluid flow from said reservoir through said conduit to said outlet and prevents fluid flow from said second inlet through said conduit to said outlet; a second detector arranged to

detect fluid flow into said conduit from said second inlet; and an activator arranged to control the operation of said first and second valves.

While the apparatus of the invention, the "applicator", is primarily intended for the delivery of hyperpolarized gases into the respiratory tract of a subject and will be described in that context below, it is also suitable for the bolus delivery of other one or more phase fluids, e.g. liquids, solid-in-liquid suspensions, gas-in-liquid dispersions, aerosols, gases, gas mixtures, powder-in-gas dispersions, etc. as mentioned above. However, hereinafter such "liquids" will simply be referred to as gases and liquid flow and liquid inlets, etc. will be referred to as gas flow and gas inlets, etc.

The primary aim of the applicator of the invention is the introduction of different gases during an intake of breath, in which situation a mixture of the types of gases should to a large extent be avoided. Fig. 1 of the accompanying drawings illustrates this for two different gases in schematic form. A hose (1) is initially filled with a first type of gas (2), such as air. This is followed by a second gas type (3), e.g. hyperpolarized ^3He, and in turn by the original type of gas (4). When the contents of the hose are inhaled during a breath, this gas sequence passes unmixed into the lungs, provided that no intermixing takes place due to turbulence, or due to excessively high flow velocities. Depending on the placement and volume of the gas bolus (3) in the hose, it is therefore possible for a defined volume of gas to be placed in a specific part of the lung.

The applicator of the invention is desirably equipped with a third valve which serves to prevent gas flow back to the second valve from the outlet, e.g. by directing it to a second outlet (e.g. a vent) or to a second reservoir, for example for the collection of ^3He

for reuse.

This third valve is preferably arranged to operate to prevent such flow back when the subject exhales and may be controlled by the activator or may be a passive valve operated automatically by the reversal of gas flow at the outlet. Optionally, the second valve may have a third setting in which gas flow from the outlet is prevented from passing to the first reservoir or to the second inlet and is directed instead to a second outlet or to a second reservoir; in this arrangement the third valve is unnecessary.

The first reservoir may be any variable volume reservoir, e.g. a barrel with a movable piston (ie. as in a syringe), a flexible sack, a bellows, etc. In a particularly convenient embodiment however it takes the form of an expandable container (e.g. a folding bellows for example made of plastic, preferably a helium tight film or a plastic coated with such a film) disposed within a rigid container provided with a venting aperture to which the first detector is attached. Gas flow into or out of the expandable container will cause a corresponding gas flow through the venting aperture and thus allow the gas flow in and out of the expandable container to be detected and measured indirectly.

In a particularly preferred embodiment of the applicator, gas flow into the second inlet is from a respirator. In this embodiment it is especially preferred that, when the second valve is in its second setting, the gas flow from the respirator should be redirected to exert pressure on the exterior of the variable volume reservoir so that the gas flow from that reservoir to the subject should be at the same pressure as the earlier/later gas flow from the respirator to the subject. It is also preferred that the applicator should include a detector, e.g. a differential pressure detector, that will detect when the variable volume reservoir has reached its minimum volume whereupon the

second valve may be returned to its first setting.

In certain circumstances, it may be desirable to administer different fluids (gases) from the variable volume reservoir, either separately or mixed together. In this event, the conduit should be provided with a further (third) inlet and a further (fourth) valve arranged to prevent or permit gas flow from the third inlet through the conduit and into the variable volume reservoir. Operation of the applicator so as to administer this further fluid via the variable volume reservoir may be equivalent to operation to administer fluid from the first inlet and the activator is preferably arranged to control the fourth valve too.

The operation of the activator in the applicator of the invention is preferably controlled by a controller (e.g. a computer) in response to signals from the detectors and to the settings input by the operator, e.g. desired bolus size and placement.

Thus in one embodiment, the invention provides a device for the exact application of gaseous substances transported in the gas into the lungs and respiratory tracts, which is provided with the following:

- a first inlet (203) for the introduction of a first gaseous substance, in particular a gas with polarised atoms (nuclei);
- a metering device (230,231) connected to the first inlet (203) for the metered administration of the volume to be applied of the first gaseous substance;
- a second inlet (301,305) for the introduction of a second gaseous substance, in particular air or an oxygen-containing gas;
- a measuring device (304) for measuring the volume of the second gaseous substance introduced via the second inlet (301,305);
- an outlet (241,243) for the first and second gaseous substances;
- a switchover valve (240), connected on the one

hand with the metering device (230,231) and the second inlet (301,305), and, on the other, with the outlet (241,243), for the optional connection of the outlet (241,243) with the second inlet (301,305) in a first valve setting, and with the metering device (230,231) in a second valve setting;

- the metering device (230,231) having an expandable container (231) connected to the first inlet (203) and arranged in a housing (230) which is provided with at least one venting aperture (235,236) to which a further measuring device (232,244) is connected for measuring the gas which flows out of the housing (230) during expansion of the container (231) and/or flows into the housing (230) during contraction of the container (231); and

- a control unit (220) connected to the two measuring devices (304,232,244) and the switchover valve (240), and which:

- controls the inflow of a volume of the first gaseous substance into the expandable container (231) of the metering device (230,231) as a function of the quantity of the gas displaced from the housing (230) of the metering device (230,231) measured by said further measuring device (232, 244),

- switches the switchover valve (240) from the first valve setting to the second valve setting as a function of the quantity of the second gaseous substance measured by the first mentioned measuring device (304), or after the expiry of a specific period of time, and

- switches the switchover valve (240) from the second valve setting to the first valve setting as a function of the quantity of the gas flowing into the housing (230) of the metering device (230,231) measured by said further measuring device (232,244).

The valves, conduits etc. of the applicator are preferably so constructed that linear flow of the gases following the second valve prevails, ie. to avoid

turbulence which would diffuse the bolus, mixing the different gas types.

The applicator desirably is arranged to permit different bolus volumes, and to permit placement of the bolus at any desired part of the entire breath intake. Moreover it preferably will be arranged to permit a single application or a sequence of applications in which, for example, the bolus volume, the bolus placement, the respiration volume, etc. may be varied. Furthermore, it is desirable for the applicator to be arranged to permit administration of gas boli of either a single gas or a gas mixture, e.g. a mixture of a hyperpolarised gas such as ^3He with a gas which does not shorten the relaxation times of the hyperpolarised gas, e.g. a gas such as nitrogen. In such a case, the non-relaxing gas (e.g. N_2) will generally be filled into the variable volume reservoir first and then mixed with a selected quantity of hyperpolarised ^3He immediately after. A long bolus of diluted ^3He may then be administered, e.g. for gas flow studies.

Desirably the operation of the applicator, ie. the production of a gas sequence through the outlet, should not noticeably interfere with or appreciably interrupt the subject's respiration.

Furthermore, the gases used, e.g. ^3He, may be expensive and the applicator is preferably arranged for their recovery.

From the clinical point of view, a distinction may be drawn between three types of respiration:

(1) the free (unhindered) spontaneous respiration under an individual's own efforts;

(2) spontaneous respiration assisted by a respirator;

(3) controlled respiration by means of a respirator.

Respirators can control the respiration by pressure control or flow control; ie. in respiration form (3),

during inhalation, either the pressure or the gas flow is regulated. While with spontaneous respiration the volume of the air inhaled varies from time to time, with volume-controlled respiration by means of a respirator the same respiration gas volume is always introduced. All these forms of respiration can be used with the invention described here.

For the embodiment of the invention for the introduction of hyperpolarised helium-3 gas (^{3}He), for ^{3}He MRI, several further features are desirable and will be described after a brief summary of the special features of ^{3}He MRI.

The nuclei of the ^{3}He atoms carry a spin of the quantum number I = ½, with which a magnetic moment μ is associated. These moments orientate themselves, in the presence of an external magnetic field, parallel or anti-parallel to the lines of the magnetic field. However, there is an imbalance between the number of the atoms with magnetic moments parallel and anti-parallel. This is described by the polarisation equations given above where B_o is the magnetic field strength (more precisely, the magnetic flux density); $k = 1.38 \times 10^{-23}$ J/K, the Boltzmann constant; and T is the temperature in Kelvin. For ^{3}He, the magnetic core dipole moment $\mu = 1.075 \times 10^{-26}$ Am^2, so with typical fields in MRI apparatus of B_o = 1.5 Tesla and T = 310 K, the polarisation $P = 3.8 \times 10^{-6}$. With a gas density under normal conditions, ie. of $p = 2.33 \times 10^{19}$ atoms/cm^3 (at 310 K and 1.013 bar gas pressure), this polarisation is not sufficient to obtain images of gas distribution in hollow spaces with the aid of MRI. The MR resonance signals are too weak.

The ^{3}He polarisation can, however, be raised to values close to 1, at ambient temperature and with low magnetic fields of the order of magnitude of mT; i.e. well above the Boltzmann equilibrium polarisation. The process is known as "optical pumping", and the physical principles, as well as the technical realisation, are

described by Colegrove et al. Phys. Rev. 132: 2561-2572 (1963), Walters et al. Phys. Rev. Lett. 8: 439-442 (1962), Schearer et al. Phys. Rev. Lett. 10: 108-110 (1963), Eckert et al. Nucl. Instr. & Meth. A320: 53-65 (1992), Becker et al. Nucl. Instr. & Meth. A346: 45-51 (1994), Heil et al. Phys. Lett. A201: 337-343 (1995), Becker et al. Journal of Neutron Research 5: 1-10 (1996) and Surkau et al. Nucl. Instr. & Meth. A384: 444-450 (1997). Densities of polarised spins p x P are attained, which are 1 to 2 orders of magnitude above those of the polarised protons in the tissue water or fatty tissue at B_o = 1.5 Tesla and at Boltzmann equilibrium. (Usually, polarised protons serve in MRI as the signal source, ie. in ^{1}H-MRI).

With nuclear magnetic resonance, the magnetic moments are excited perpendicular to B_o as a result of which a magnetic resonance signal is induced in a suitable reception coil. This occurs at the expense of the polarisation, which is partially or totally destroyed, depending on how strongly the magnetic moments are deflected from the direction of the field during the nuclear resonance excitation. While the Boltzmann polarisation used in the ^{1}H-MRI is restored again with a characteristic relaxation time T_1 of 0.3 to 3 seconds, in comparison the ^{3}He hyperpolarisation irrevocably decays with a characteristic relaxation time T_1 of 10 to 30 seconds from its high initial value in the lung to the very much smaller Boltzmann equilibrium value.

With ^{3}He MRI in high field (B_o = 1.5 Tesla), RF excitation (nuclear resonance excitation) is repeated according to the matrix size required for the image. However, for a lung image there is only one ^{3}He gas filling available. Accordingly, the magnetic moments at each ^{3}He nuclear resonance excitation are only slightly deflected from the B_o-axis, by an angle α of, for example, 2°, in order, after each excitation, to save

$\cos(\alpha)$ (for $\alpha=2°$, $\cos(\alpha)$ = 99.9%) of the original polarisation for the subsequent RF excitation. (In other words a spin-echo sequence with a low flip angle, e.g. a RARE sequence, or a gradient echo sequence, such as a FLASH sequence, is used.) This emphasises the need for externally-derived hyperpolarisation of the ^{3}He gas to be retained during the application.

In addition to nuclear spin excitation, there is a series of effects which can destroy the hyperpolarisation of the ^{3}He gas. Mention may be made, as the most important of these, of relaxation due to magnetic field gradients, of relaxation on the walls of the gas container, and of the admixture of oxygen (O_2). The relative longitudinal gradients of the magnetic field of a conventional commercial tomograph, at $(dB_z/dz)/B_o$ of about 10^{-7}/cm, are very small. As the transverse gradient, $(dB_r/dr)/B_o$, is of similar magnitude, the result at a gas pressure of 1 bar is a T_1 value:

$$1/T_1 = \left(1.75x10^4 \left(\frac{dB_r}{dr}\frac{1}{B_o} \right)^2 . \frac{1}{p}\frac{cm^2 bar}{h} \right)$$

which is about 10^{-9} h^{-1}.

In other words such gradients do not invoke any measurable T_1 relaxation. Even the maximum permissible gradient fields for the imaging, where $(dB_r/dr)/B_o$ is about $1.67x10^{-4}$/cm, lead at p = 1 bar to relaxation rates of only $1/T_1 = 5x10^{-4}$/h and are negligible. However, at the aperture of the magnet of an MRI apparatus, gradients occur of up to $(dB_r/dr)/B_o$ = approx. 10^{-1}/cm, corresponding to a relaxation time of T_1 = approx. 21 s. Accordingly, hyperpolarised ^{3}He gas should be transported through this region rapidly, e.g. in time Δt of less than a second, in order to maximize the remaining polarisation P ($P = P_o \exp(-\Delta t/T_1)$, where P_o is the initial polarisation), e.g. to keep it above 0.95 (95%),

and so retain as much of the polarisation as possible.

Ferromagnetic substances distort homogeneous magnetic fields, and lead to gradients which are very much stronger. These should therefore preferably be avoided as materials for the construction of an applicator. Non-ferromagnetic substances such as, for example, plastics, titanium, or glass, leave the magnetic field undistorted, and are in principle suitable. They differ, however, in their wall relaxation properties if used as gas container materials. To preserve ^3He polarisation over lengthy periods of time, special glass containers which leave relaxation times T_1 ranging from hours to days are preferred (see Heil et al., supra). Valves which come into contact with hyperpolarised gases are preferably made of titanium (see Becker et al. (1994) supra). Plastics may be used but are of limited suitability as ^3He may be able to penetrate their porous structures and become depolarised in them. Typical relaxation times are in the minute range. However, in the nuclear spin tomograph itself all moving parts will normally be made of plastic, because moving metal parts have proved to cause interference with nuclear resonance tomography.

In addition to this, paramagnetic impurities, including gaseous oxygen, will preferably be excluded at least from the portions of the appicator between the reservoir and the second valve. Oxygen results in a strong relaxation effect; thus at 299K:

$$T_1 = 2.2s \cdot \frac{Amagat}{[O_2]}$$

where $[O_2]$ is the oxygen density in Amagat units in the ^3He gas (see Saam et al., Phys. Rev. A 52: 862-865 (1995)). As a result, relatively thick conduit etc. walls may be desired so that oxygen may be expelled, for example by flushing with nitrogen gas. When fitting a

fresh source of ^3He to the applicator, it is also desirable to flush the ^3He inlet ((203) in Figure 2) with a small quantity, e.g. about 20 mL, of ^3He, to remove any air.

Where the applicator is to be used with an animate subject, aspects of hygiene should also be taken into account. Parts which come in contact with the respiration gas of the patient being examined should preferably be disposable or be capable of being sterilised or disinfected. The materials used for such "contact" components are therefore desirably shape stable at temperatures of up to 120°C.

Desirably all the component parts of the applicator are of non-magnetic materials, especially non-metallic materials, more preferably electrically non-conductive materials, e.g. plastics. Moving parts particularly are desirably made of plastics.

The measuring device which determines the quantity of gas which flows into or out of the housing of the metering device at contraction and expansion respectively preferably comprises a flowmeter connected to a venting aperture of the housing, and a differential pressure gauge connected to a ventillation aperture of the housing, which measures the differential pressure between the interior of the housing and the outlet of the applicator. The switchover valve (the second valve) may then be switched over in response to the measured value.

With an appropriate selection of materials, the applicator of the invention can be arranged within a nuclear spin tomograph. (Appropriate selection of materials in this regard has already been commented upon above).

For hyperpolarised gas administration it is desirable that the dead space in the apparatus, especially between first inlet and variable volume reservoir and between that reservoir and the outlet, is

minimised. This assists in reducing unnecessary loss in polarisation by time delay or wall contact.

Besides hyperpolarised ^{3}He, the applicator may be used with other hyperpolarised gases, e.g. ^{129}Xe and compounds containing other hyperpolarised I = ½ nuclei (e.g. ^{13}C, ^{15}N or ^{29}Si).

Viewed from a further aspect the invention provides a method of magnetic resonance imaging in which a fluid (preferably gaseous, especially a hyperpolarised gas) MR imaging agent is administered in a bolus to a subject and a MR image (preferably a non proton MR image) of at least a part of said subject into which said agent distributes is generated, characterised in that said fluid is administered using an apparatus according to the invention, the fluid preferably being administered into the respiratory system of the subject.

Imaging according to the method of the invention may be performed conventionally.

The bolus administration conveniently takes up 2 to 100%, more preferably 5 to 30% in time of the breath intake, and may be positioned at any stage of that intake. The gas administered, if hyperpolarised is preferably polarised to a value of P of at least 5%, preferably at least 10%.

Publications referred to herein are hereby incorporated by reference.

Embodiments of the invention will now be described further with reference to the accompanying drawings, in which:

Fig. 1 is a schematic representation of a gas bolus arranged between two other gas flows in a hose;

Fig. 2 is a schematic view of an applicator according to the invention;

Fig. 3 is a schematic view of the applicator of Fig. 2 in the operating position in which air is being fed to the subject patient;

Fig. 4 is a schematic view of the applicator of

Fig. 2 in the operating position in which the subject patient is being supplied with the bolus of gas, e.g. hyperpolarised ^3He;

Fig. 5 is a scehmatic view of an alternative applicator, equivalent to that of Fig. 3 but with a passively-actuated non-return valve to prevent the backflow of air into the outlet of the applicator; and

Fig. 6 is a schematic view of a further applicator in the same operating position as that of Figure 4;

Fig. 7 is a graph showing ^3He concentration in three simulated breaths; and

Fig. 8 is a graph showing ^3He concentration in four simulated breaths.

Fig. 2 shows with (10) an overview of the equipment modules which are used for the application of ^3He boli. The person (101) to be examined lies in the field of the nuclear spin tomograph (102). His respiration air passes via a hose (301) to the applicator (20), which conveys it onwards to the patient. The exhaled air can be recovered via the line (302).

For controlled respiration, the intake air can be provided from a respirator (30) under controlled conditions; this also allows for special oxygen densities to be adjusted in the respiration air. In the event of it being intended that special gases should be recovered after respiration, they can be collected, for example, in a bag (303).

The special gas boli are inserted into the respiration air by the applicator (20) which is placed within the nuclear spin tomograph, close to the patient's head. The result of this is that, except for unavoidable dead volumes in the respiration hoses, further dead volumes can be avoided. The reservoir (201-203) of hyperpolarised ^3He is considered here to be part of the applicator (20). The gas is hyperpolarised externally, and is located in the container (201), which has been filled at the supplier or manufacturer. The

container (201) consists, for example, of a glass cell with a valve (202), and can be connected via a connection flange (203) to the applicator (20). While the ^{3}He container (201) itself will allow for very long relaxation times, all other surfaces which come in contact with hyperpolarised ^{3}He should be small. When a specific gas quantity is passing through, the dwell times in the corresponding volumes are then short, and the polarisation losses which then occur are small. This is why it is desirable to place the applicator in the nuclear spin tomograph. By contrast, flushing gases such as nitrogen, for example, can be introduced from externally located cylinders (210) via lines (211). The applicator (20) itself is controlled by a computer (220), which is connected to the applicator (20) via electrical, pneumatic, and hydraulic instrumentation and control lines (221).

Fig. 3 shows a schematic diagram of the applicator (20). The components inside the area defined by the dotted line are arranged in the tomograph field. Their materials and dimensions should preferably satisfy the requirements indicated earlier. In particular, all the cross-sections conveying respiration gas are preferably designed with a relatively large cross-section surface area corresponding to the area of a circle of a diameter of, for example 22 mm. This permits a laminar current in flows of up to 560 ml/s.

Before the application of the desired gas bolus, the patient inhales via the line (301/305), the valve (240), and the line (241) and exhales via the line (302). At the moment of the administration of the bolus, when the gas quantity (2) (Fig. 1) is introduced into the line (241), the normal gas flow from the lines (301) and (305) is interrupted by the valve (240), and, instead of this, a volume of gas from a bellows (231) is conveyed to the patient (see Fig. 4). These bellows (231) are located in a housing (230). With the

switchover valve in the switched-over position (relative to the representation of the valve (240) in Fig. 3, displaced to the right), the bellows are connected to the line (305). If the applicator (20) is connected to a respirator, then in this case the housing (230) is subjected to the preliminary pressure of the respiration air from the respirator. As a consequence, the bellows (231) are pressed empty, and the gas volume originally filled into it via the line (206), valve (240), and line (241) is conducted to the patient. If the bellows (231) are emptied (which is detected by means of a pressure rise at the differential pressure sensor (244)), the valve (240) is reset, and the normal respiration flow to the patient is continued (see Fig. 3). The differential pressure sensor (244) is connected via the line (242) to a ventilating aperture (235) in the housing (230).

Where hyperpolarised gas is being administered, the exhaled air preferably should not flow back into the applicator. When a respirator is being used, it monitors the inhalation and exhalation phase, and allows gas to pass freely via the line (301) accordingly, or opens a valve (not shown) at the end of the line (302). For this operating mode, it is sufficient for the line (241) and (302) to be connected directly to the mouth by means of Y-piece, and for the gas to be applied via a mouthpiece.

If the applicator (20) is being used without a respirator, the patient normally sucks air in via the line (301) and (305), the valve (240), and the line (241). In order to prevent a backflow of the air into the applicator (20), a passively-actuated valve (245) (Fig. 5) is accordingly used. At exhalation, this blocks the line (241) and clears the line (302). In this operating mode, the patient sucks the bellows (231) empty after the valve (240) is switched over. In this case, too, a pressure differential at the differential pressure sensor (244) causes valve (240) to switch back.

In Fig. 6 an applicator is shown which is provided with passively activated valves (310) and (311) in the respirator line (301) and the exhalation line (302). This can be done by using a Y-piece in combination with these valves and in this way possible relaxation of hyperpolarised gas by the commercially available valves such as valve (245) of Fig. 5 may be avoided.

In order to monitor the patient's respiration process, a flowmeter (304) is inserted into the inspiration branch (lines 301,305). The filling of the bellows (231) is effected during the expiration phase either from external gas cylinders via the line (211) or from the ^{3}He tank (201), the valve (202) of which has been opened after being flanged on. Gas is filled into the bellows (231), previously pressed empty, via the computer-controlled valves (212) and (204) respectively. The quantity is determined in accordance with the bolus quantity which is to be applied. In this context, the gas flow is adjusted by means of metering valves (213) and (205) respectively, in such a way that the gas quantity conveyed is filled into the bellows (231), e.g. in about 0.5 seconds. The setting of the metering valve (205) is determined in accordance with the preliminary pressure in the line (211) or in the tank (201) (in relation to atmospheric pressure), which in the case of nitrogen is usually 4 bar, and in the case of ^{3}He 2 to 0 bar, depending on how much gas remains in the tank (201).

On filling the reservoir (231), air is expelled from the housing (230) and escapes via flowmeter (232), which is connected to the venting aperture (236) and the valve (233) and line (234) which is opened in this phase. The measured data from the flowmeter is recorded when the bellows (231) are filled, and temporally integrated. The displaced air quantity determined n this way is equivalent to the gas quantity filled into the bellows (231). The latter quantity is therefore

indirectly determined, which is of advantage in the handling of polarised gases, especially in view of their relaxation sensitivity in contact with certain materals. As a function of this measured volume, with filling times of 0.5 s, gas quantities can be filled in a reproducible manner with a relative error of less than 5%.

Temporal delays due to valve switching times may be compensated for as the switching times of the valves can be determined in advance from known gas flows, and the valves may be actuated early, by the known delay times. This means, in particular, that the moment of administration of the bolus can be effected with a precision of within 20 ms, which restricts the uncertainty of pre-inhaled gas quantities at an assumed respiration flow of 500 ml/s to less than Δq <500 ml/s. 20 ms, ie. less than 10 ml. It should be noted that in all cases the gas from the dead volume in line (241) between the valve (240) and the patient must be pre-inhaled before the bolus which is to be applied reaches the patient. Accordingly, the applicator (20) can to advantage be located directly next to the patient's head. The dead volume in the line (241) may then be as little as 60 ml in the embodiment described.

The valves, metering valves, and flowmeters used may, as far as possible, be conventional commercial components. The valves (204) and (233) in this embodiment may be hydraulically operated, and adapted to the required dimensions, and may be manufactured from appropriate selected materials. The valve (240) is conveniently hydraulically actuated, and advantageously designed in such a way that, during the switchover phase, all the inlets and outlets are connected. This then ensures that the gas flow to the patient will not be interrupted when the valve is switched.

Test measurements of the polarisation loss of the ^{3}He on transfer through the applicator have been

conducted. The relaxing effect of the relevant components of the applicator was measured with the aid of NMR methods. The bellows, made of He-tight, film after being well flushed of any oxygen residue with pure nitrogen gas, featured relaxation times of 20 to 40 minutes. Because the gas is stored into the bellows for only one breath, for at most a few seconds before the application, polarisation losses are accordingly < 1%. Location dependent relaxation times measured in the valve (240) varied between 10 and 20s, so that, when flowing through, within 1s, more than 90% of the ^3He polarisation should be retained. When filling the bellows, and when flowing through additional lines, no demonstrable polarisation losses occur. In total, more than 90% of the original polarisation reaches the patient.

Fig. 7 shows how sharp and how placeable the boli produced using the applicator may be. Three simulated breath intakes, (a), (b) and (c), with ^3He bolus placement at different points in the breath intakes were generated and the ^3He content of the gas leaving the outlet (mouthpiece) was measured indirectly by adding carbon dioxide to the respirator air and measuring the CO_2 content of the gas at the mouthpiece using a conventional CO_2 meter. The ^3He contents for the three simulated breaths are shown superimposed.

Fig. 8 shows how the bolus size (duration) may be varied. Four simulated breath intakes, (d), (e), (f) and (g) with increasingly larger ^3He boli, were generated and the ^3He content was determined as for Fig. 7 above. As with Fig. 7 the results are shown superimposed.

Claims

1. An apparatus for fluid administration comprising: a variable volume fluid reservoir and a fluid conduit leading therefrom to a fluid outlet, a first fluid inlet and a second fluid inlet; a first detector arranged to detect fluid flow between said conduit and said reservoir; a first valve arranged to permit or prevent fluid flow from said first inlet through said conduit into said reservoir; a second valve which in a first setting permits fluid flow from said second inlet through said conduit to said outlet and prevents fluid flow from said reservoir through said conduit to said outlet and in a second setting permits fluid flow from said reservoir through said conduit to said outlet and prevents fluid flow from said second inlet through said conduit to said outlet; a second detector arranged to detect fluid flow into said conduit from said second inlet; and an activator arranged to control the operation of said first and second valves.

2. An apparatus as claimed in claim 1 wherein said reservoir is a flexible container disposed within a rigid container having a venting aperture and where said first detector is arranged to detect fluid flow through said venting aperture.

3. An apparatus as claimed in either of claims 1 and 2 further provided with a valve serving to direct fluid flow from said outlet into said conduit to a second outlet or to a second reservoir and to prevent said fluid flow from reaching said variable volume reservoir.

4. An apparatus as claimed in any one of claims 1 to 3 further comprising a source of a hyperpolarised gas attached to said first inlet.

5. An apparatus as claimed in any one of claims 1 to 4 further comprising a respirator attached to said second inlet.

6. An apparatus as claimed in any one of claims 1 to 5 further comprising a third inlet and a third valve arranged to permit or prevent fluid flow from said third inlet into said variable volume reservoir and wherein said activator is also arranged to control the operation of said third valve.

7. An apparatus as claimed in any one of claims 1 to 6 wherein the internal surface of said variable volume reservoir and all surfaces contactable by fluid entering said conduit through said first inlet and leaving said conduit through said outlet are of a non-magnetic material.

8. An apparatus as claimed in claim 7 wherein said non-magnetic materials are selected from glass, titanium and plastics.

9. An apparatus as claimed in any one of claims 1 to 8 wherein the construction of said conduit between said second valve and said outlet is such that fluid flow therethrough is essentially laminar.

10. An apparatus as claimed in any one of claims 1 to 9 constructed of non-magnetic materials.

11. An apparatus as claimed in any one of claims 1 to 10 having:

- a first inlet (203) for the introduction of a first gaseous substance, in particular a gas with polarised atoms (nuclei);
- a metering device (230,231) connected to the first inlet (203) for the metered administration of the

volume to be applied of the first gaseous substance;

- a second inlet (301,305) for the introduction of a second gaseous substance;

- a measuring device (304) for measuring the volume of the second gaseous substance introduced via the second inlet (301,305);

- an outlet (241,243) for the first and second gaseous substances;

- a switchover valve (240), connected on the one hand with the metering device (230,231) and the second inlet (301,305), and, on the other, with the outlet (241,243), for the optional connection of the outlet (241,243) with the second inlet (301,305) in a first valve setting, and with the metering device (230,231) in a second valve setting;

- the metering device (230,231) having an expandable container (231) connected to the first inlet (203) and arranged in a housing (230) which is provided with at least one venting aperture (235,236) to which a further measuring device (232,244) is connected for measuring the gas which flows out of the housing (230) during expansion of the container (231) and/or flows into the housing (230) during contraction of the container (231); and

- a control unit (220) connected to the two measuring devices (304,232,244) and the switchover valve (240), and which:

- controls the inflow of a volume of the first gaseous substance into the expandable container (231) of the metering device (230,231) as a function of the quantity of the gas displaced from the housing (230) of the metering device (230,231) measured by said further measuring device (232, 244),

- switches the switchover valve (240) from the first valve setting to the second valve setting as a function of the quantity of the second gaseous substance measured by the first mentioned measuring device (304),

or after the expiry of a specific period of time, and

- switches the switchover valve (240) from the second valve setting to the first valve setting as a function of the quantity of the gas flowing into the housing (230) of the metering device (230,231) measured by said further measuring device (232,244).

12. An apparatus as claimed in any one of claims 1 to 10 further comprising a computer control means.

13. A method of magnetic resonance imaging in which a fluid MR imaging agent is administered in a bolus to a subject and a MR image of at least a part of said subject into which said agent distributes is generated, characterised in that said fluid is administered using an apparatus according to any one of claims 1 to 12.

14. A method as claimed in claim 13 wherein said MR imaging is ^{3}He-NMR imaging.

FIG.1

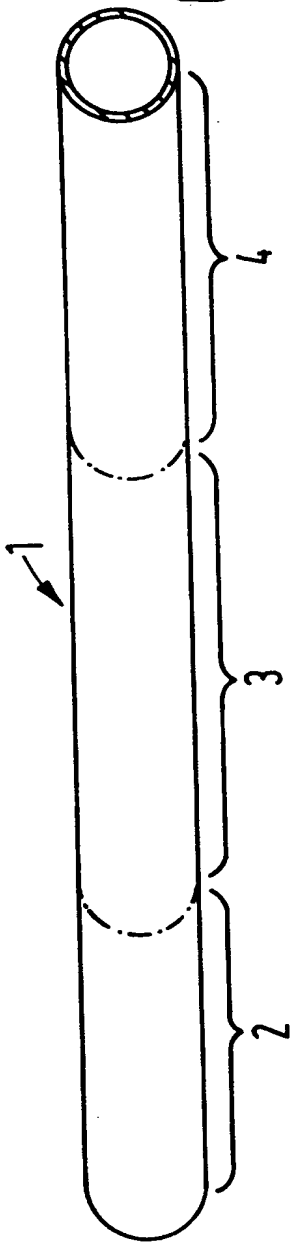
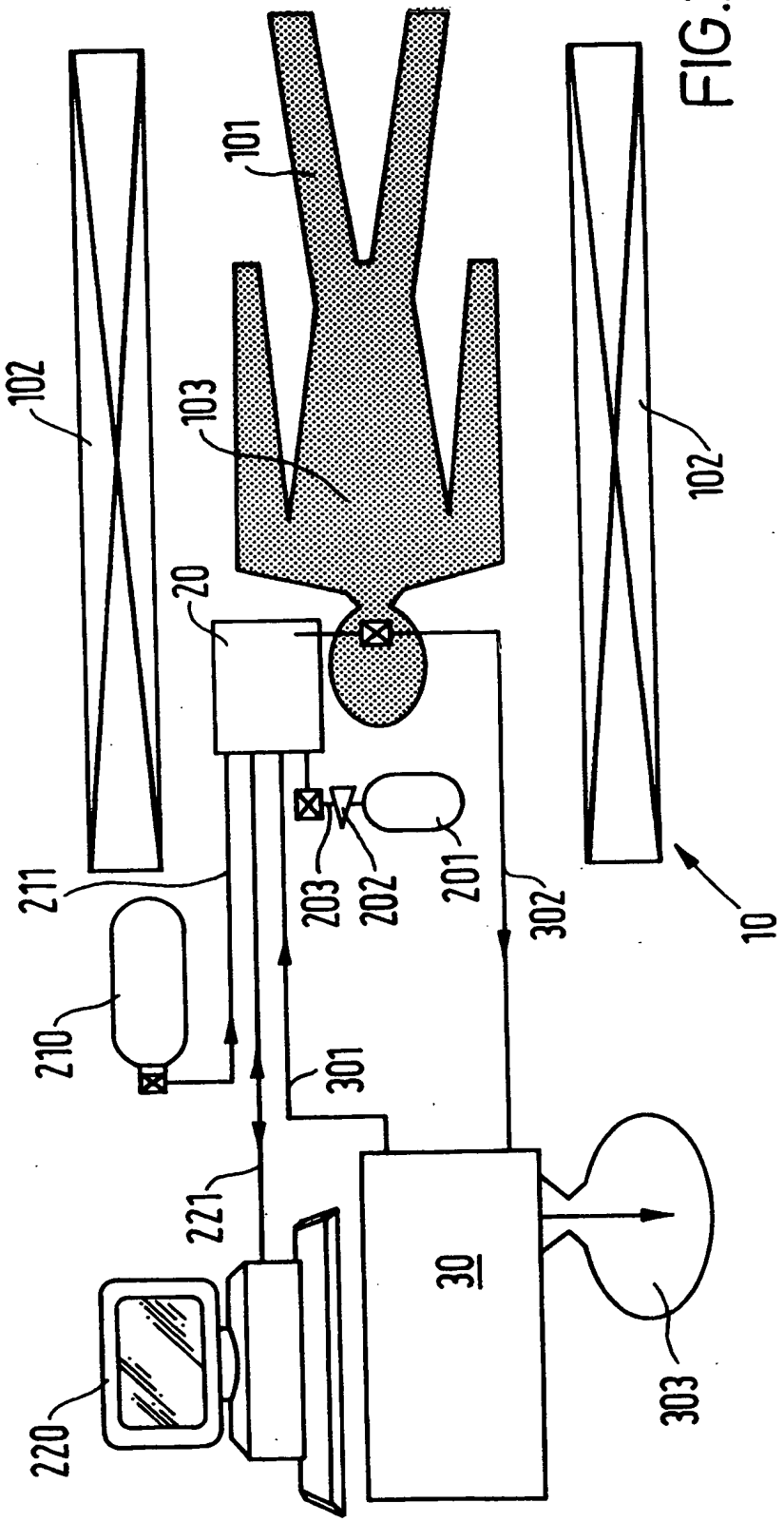


FIG.2



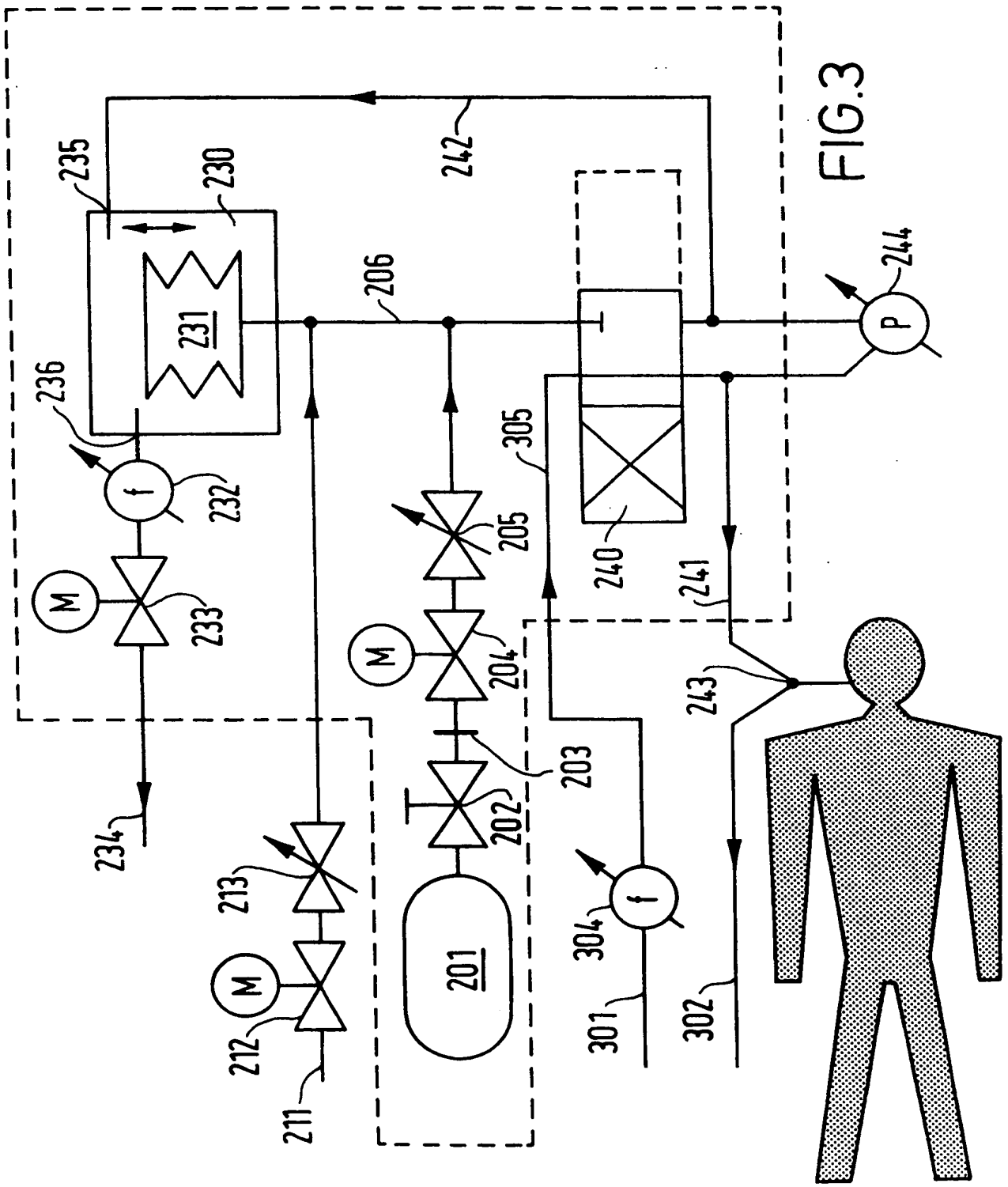


FIG.3

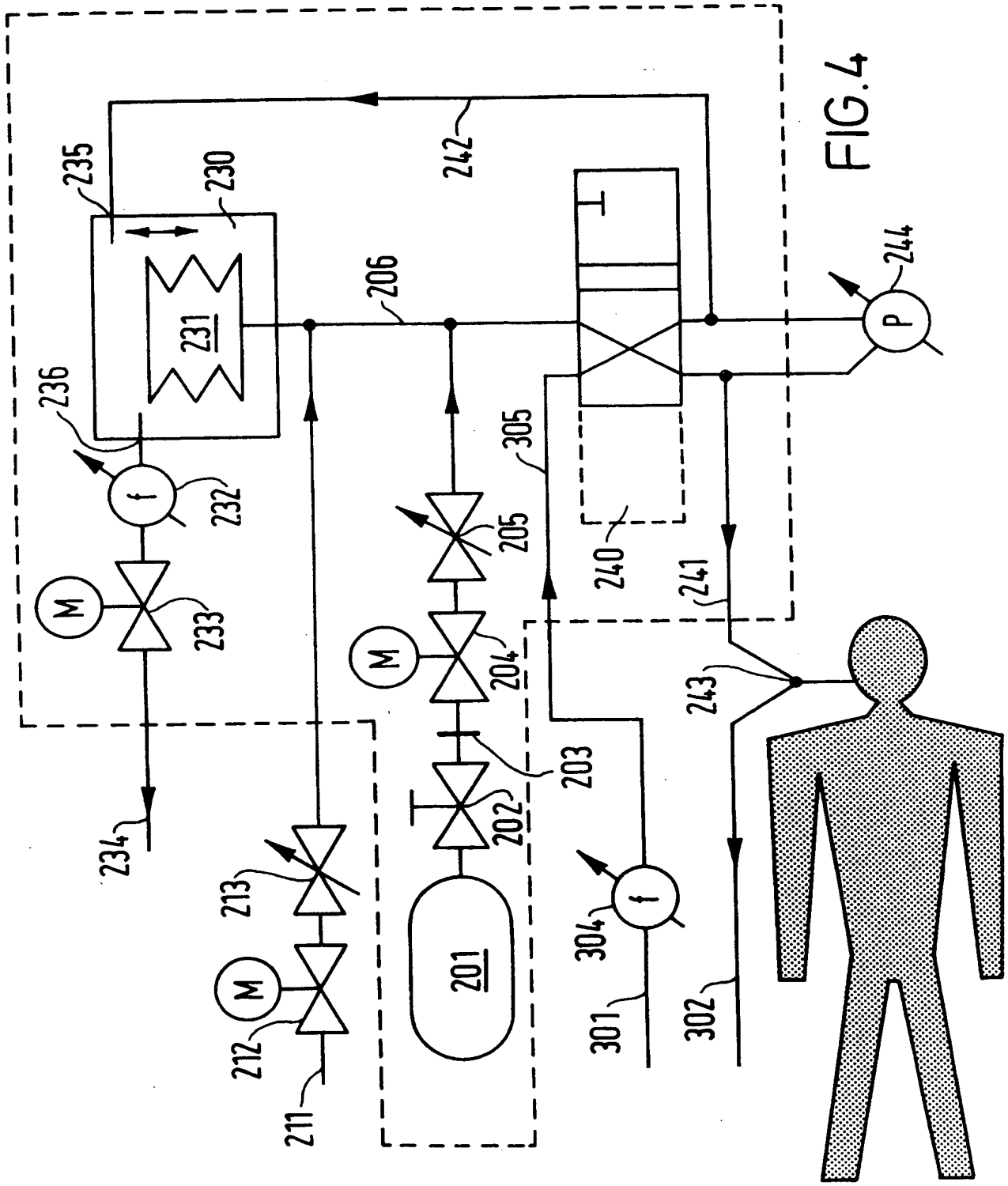


FIG.4

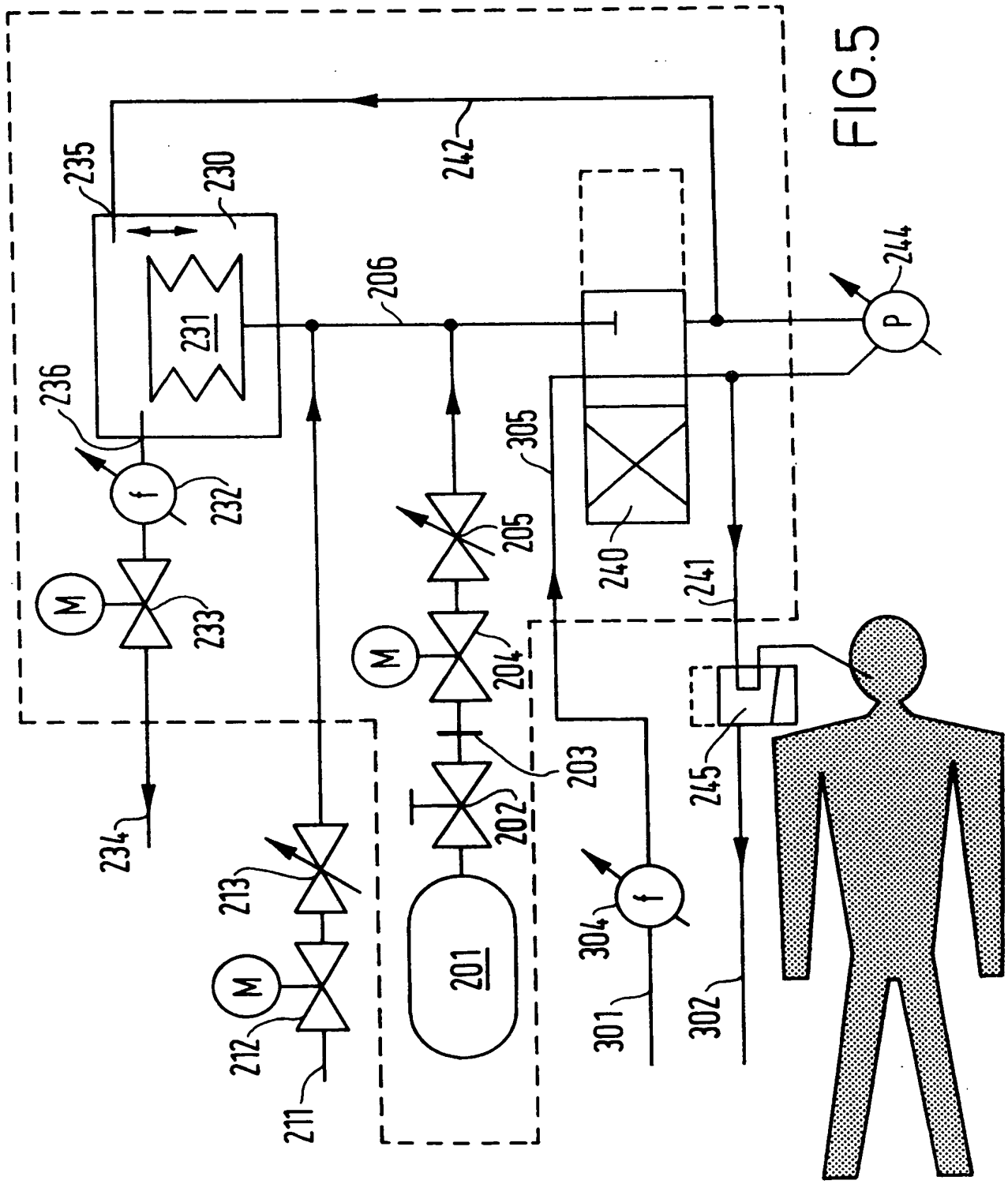


FIG.5

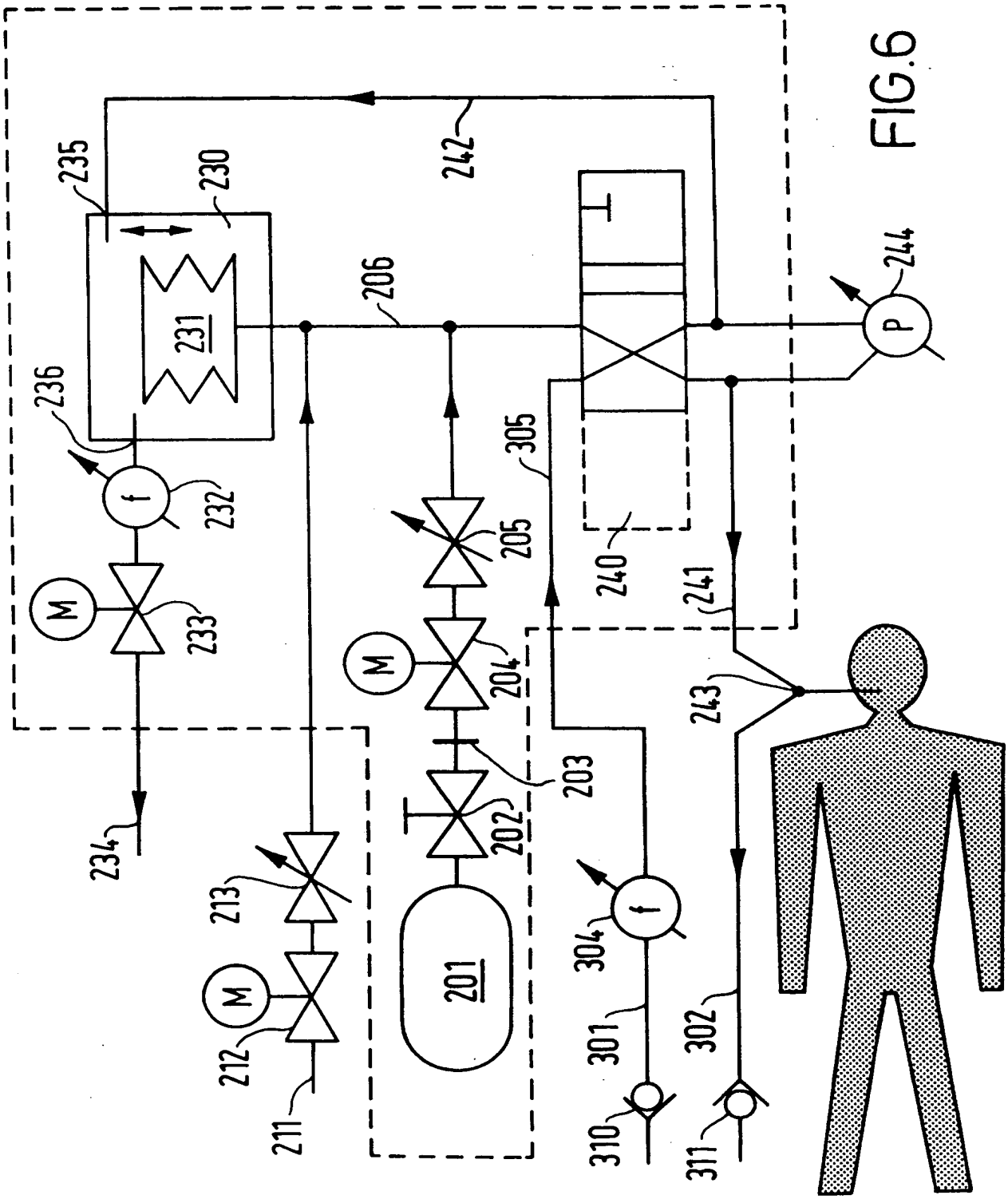


FIG.6

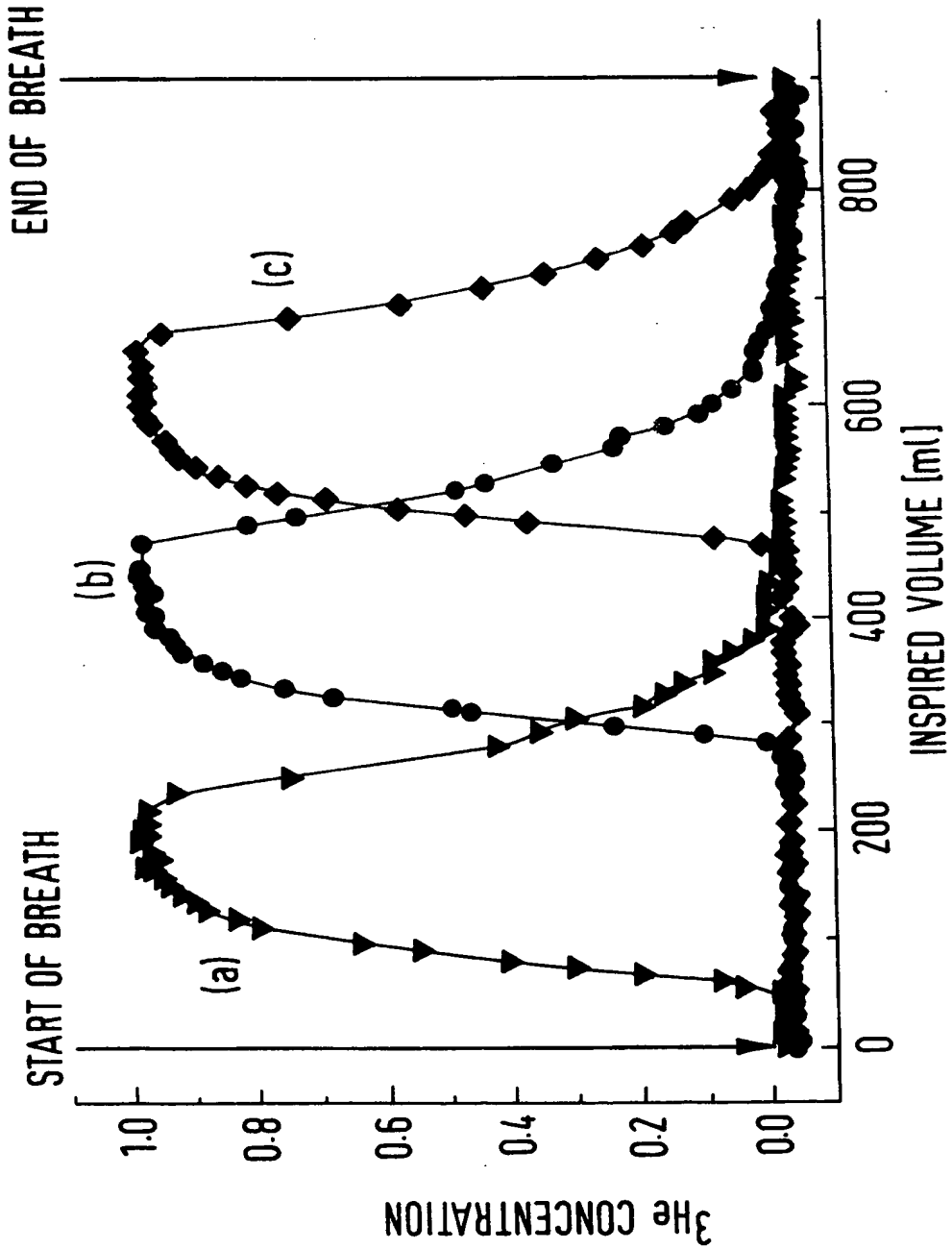


FIG.7

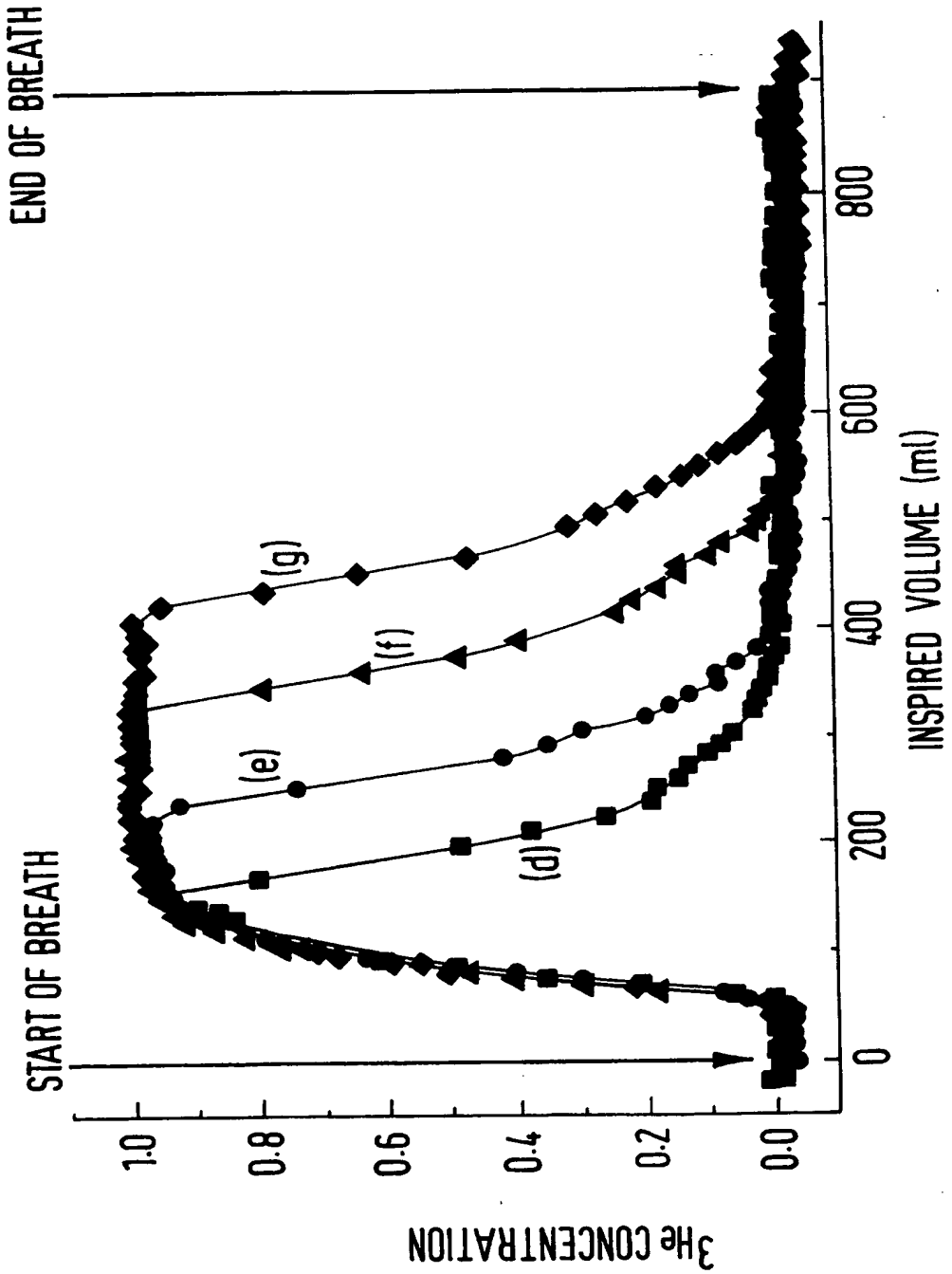


FIG.8

INTERNATIONAL SEARCH REPORT

Internation .pplication No
PCT/EP 98/07516

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61B5/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M A61B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 932 401 A (PERKINS WARREN E) 12 June 1990 see column 3, line 55 - column 5, line 17; figure 1	1,3
A	US 4 169 465 A (HOWARD ROBERT P ET AL) 2 October 1979 see column 3, line 8 - column 4, line 21; figures	1,3,5
A	DE 196 19 471 C (SIEMENS AG) 16 October 1997 see abstract; figure 1	1,4
A	US 3 666 955 A (DOUGLAS CLAYTON H ET AL) 30 May 1972	

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 April 1999	23/04/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P B 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl, Fax: (+31-70) 340-3016	Villeneuve, J-M

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INTERNATIONAL SEARCH REPORT

Internatior. .pplication No
PCT/EP 98/07516

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 370 112 A (PERKINS WARREN E) 6 December 1994 ---	
A	US 4 810 392 A (FULTON SCOTT P ET AL) 7 March 1989 -----	

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/07516

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 13,14
because they relate to subject matter not required to be searched by this Authority, namely:

Rule 39.1(iv) PCT - Diagnostic method practised on the human or animal body

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internatior. .pplication No
PCT/EP 98/07516

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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